

chemotherapeutic agent. . .
IT 168682-53-9P 286942-97-0P
RL: PAC (Pharmacological activity); SPN (Synthetic preparation); THU
(Therapeutic use); BIOL (Biological study); PREP (Preparation); USES
(Uses)
(pharmaceutical compns. containing glutathione analogs)

=> file pctfull
COST IN U.S. DOLLARS
FULL ESTIMATED COST

SINCE FILE	TOTAL
ENTRY	SESSION
11.31	61.97

DISCOUNT AMOUNTS (FOR QUALIFYING ACCOUNTS)
CA SUBSCRIBER PRICE

SINCE FILE	TOTAL
ENTRY	SESSION
-0.75	-2.25

FILE 'PCTFULL' ENTERED AT 09:39:36 ON 14 AUG 2006
COPYRIGHT (C) 2006 Univentio

FILE LAST UPDATED: 8 AUG 2006 <20060808/UP>
MOST RECENT UPDATE WEEK: 200631 <200631/EW>
FILE COVERS 1978 TO DATE

>>> IMAGES ARE AVAILABLE ONLINE AND FOR EMAIL-PRINTS <<<

>>> NEW IPC8 DATA AND FUNCTIONALITY NOW AVAILABLE IN THIS FILE.
SEE

<http://www.stn-international.de/stndatabases/details/ipc-reform.html> >>>

>>> FOR CHANGES IN PCTFULL PLEASE SEE HELP CHANGE
(last updated April 10, 2006) <<<

>>> NEW PRICES IN PCTFULL AS OF 01 JULY 2006. FOR DETAILS,
PLEASE SEE HELP COST <<<

=> s TER () (286 or 199)

64391 TER
9512 TERS
69137 TER
(TER OR TERS)

38923 286
65479 199

L15 15 TER (W) (286 OR 199)

=> s combination or combined

452833 COMBINATION
199923 COMBINATIONS
492208 COMBINATION
(COMBINATION OR COMBINATIONS)

331462 COMBINED
3 COMBINEDS

331463 COMBINED
(COMBINED OR COMBINEDS)

L16 564675 COMBINATION OR COMBINED

=> s l15 and l16

L17 14 L15 AND L16

=> s l17 not py>2001

533324 PY>2001

L18 5 L17 NOT PY>2001

=> d ibib 1-5

L18 ANSWER 1 OF 5 PCTFULL COPYRIGHT 2006 Univentio on STN
 ACCESSION NUMBER: 1999037802 PCTFULL ED 20020515
 TITLE (ENGLISH): METHODS TO IDENTIFY MYELOSTIMULANTS
 TITLE (FRENCH): METHODES D'IDENTIFICATION DE MYELOSTIMULANTS
 INVENTOR(S): KAUVAR, Lawrence, M.
 PATENT ASSIGNEE(S): TELIK, INC.
 LANGUAGE OF PUBL.: English
 DOCUMENT TYPE: Patent
 PATENT INFORMATION:

NUMBER	KIND	DATE
WO 9937802	A1	19990729

DESIGNATED STATES
 W: AU CA GD IN JP AT BE CH CY DE DK ES FI FR GB GR IE IT
 LU MC NL PT SE

APPLICATION INFO.: WO 1999-US765 A 19990114
 PRIORITY INFO.: US 1998-09/010,390 19980121

L18 ANSWER 2 OF 5 PCTFULL COPYRIGHT 2006 Univentio on STN
 ACCESSION NUMBER: 1997025342 PCTFULL ED 20020514
 TITLE (ENGLISH): TETHERED PRODRUGS BY VIRTUE OF COVALENT LINKAGE WITH
 ANALOGS OF GLUTATHIONE
 TITLE (FRENCH): PRECURSEURS DE MEDICAMENTS LIES PAR UNE LIAISON
 COVALENTE A L'AIDE D'ANALOGUES DE GLUTATHIONE
 INVENTOR(S): LYTTLE, Matthew, H.;
 KAUVAR, Lawrence, M.
 PATENT ASSIGNEE(S): TERRAPIN TECHNOLOGIES, INC.
 LANGUAGE OF PUBL.: English
 DOCUMENT TYPE: Patent
 PATENT INFORMATION:

NUMBER	KIND	DATE
WO 9725342	A1	19970717

DESIGNATED STATES
 W: AU CA JP AT BE CH DE DK ES FI FR GB GR IE IT LU MC NL
 PT SE

APPLICATION INFO.: WO 1996-US20042 A 19961220
 PRIORITY INFO.: US 1996-8/582,966 19960104

L18 ANSWER 3 OF 5 PCTFULL COPYRIGHT 2006 Univentio on STN
 ACCESSION NUMBER: 1996040205 PCTFULL ED 20020514
 TITLE (ENGLISH): METABOLIC EFFECTS OF CERTAIN GLUTATHIONE ANALOGS
 TITLE (FRENCH): EFFETS METABOLIQUES DE CERTAINS ANALOGUES DE
 GLUTATHIONE
 INVENTOR(S): KAUVAR, Lawrence, M.;
 LYTTLE, Matthew, H.;
 MORGAN, Amy, S.;
 BORCH, Richard, F.
 PATENT ASSIGNEE(S): TERRAPIN TECHNOLOGIES, INC.
 LANGUAGE OF PUBL.: English
 DOCUMENT TYPE: Patent
 PATENT INFORMATION:

NUMBER	KIND	DATE
WO 9640205	A1	19961219

DESIGNATED STATES
 W: AL AM AU BB BG BR CA CN CZ EE GE HU IL IS JP KG KP KR
 LK LR LT LV MD MG MK MN MX NO NZ PL RO SG SI SK TR TT
 UA UZ VN KE LS MW SD SZ UG AM AZ BY KG KZ MD RU TJ TM
 AT BE CH DE DK ES FI FR GB GR IE IT LU MC NL PT SE BF
 BJ CF CG CI CM GA GN ML MR NE SN TD TG

APPLICATION INFO.: WO 1996-US9057 A 19960605
 PRIORITY INFO.: US 1995-8/482,645 19950607
 US 1996-8/636,516 19960419

L18 ANSWER 4 OF 5 PCTFULL COPYRIGHT 2006 Univentio on STN
 ACCESSION NUMBER: 1995009866 PCTFULL ED 20020514
 TITLE (ENGLISH): GLUTATHIONE S-TRANSFERASE-ACTIVATED COMPOUNDS
 TITLE (FRENCH): COMPOSES ACTIVES PAR LA GLUTATHIONE S-TRANSFERASE
 INVENTOR(S): KAUVAR, Lawrence, M.;
 LYTTLE, Matthew, H.;
 SATYAM, Apparao
 PATENT ASSIGNEE(S): TERRAPIN TECHNOLOGIES, INC.
 LANGUAGE OF PUBL.: English
 DOCUMENT TYPE: Patent
 PATENT INFORMATION:

NUMBER	KIND	DATE
WO 9509866	A1	19950413

DESIGNATED STATES
 W: AU CA JP AT BE CH DE DK ES FR GB GR IE IT LU MC NL PT
 SE

APPLICATION INFO.: WO 1994-US11109 A 19940930
 PRIORITY INFO.: US 1993-8/130,736 19931001
 US 1994-8/309,005 19940919

L18 ANSWER 5 OF 5 PCTFULL COPYRIGHT 2006 Univentio on STN
 ACCESSION NUMBER: 1995009865 PCTFULL ED 20020514
 TITLE (ENGLISH): GLUTATHIONE S-TRANSFERASE-ACTIVATED COMPOUNDS
 TITLE (FRENCH): COMPOSES ACTIVES PAR LA GLUTATHIONE S-TRANSFERASE
 INVENTOR(S): KAUVAR, Lawrence, M.;
 LYTTLE, Matthew, H.;
 SATYAM, Apparao
 PATENT ASSIGNEE(S): TERRAPIN TECHNOLOGIES, INC.
 LANGUAGE OF PUBL.: English
 DOCUMENT TYPE: Patent
 PATENT INFORMATION:

NUMBER	KIND	DATE
WO 9509865	A1	19950413

DESIGNATED STATES
 W: AU CA JP AT BE CH DE DK ES FR GB GR IE IT LU MC NL PT
 SE

APPLICATION INFO.: WO 1994-US10796 A 19940923
 PRIORITY INFO.: US 1993-8/130,736 19931001
 US 1994-8/130,736 19940919

=> d kwic 2-5

L18 ANSWER 2 OF 5 PCTFULL COPYRIGHT 2006 Univentio on STN

DETD However, TER 117 does not. A prodrug constructed from
 TER 117 as described in the above-referenced PCT
 application, TER 286, has the desired isoenzyme
 specificity for cells having GST complements high in the
 P1-1 isoform; however, this form of the prodrug would.
 . . .
 or acid at a temperature of from about
 00C to about 1000C, preferably at room temperELture either
 in water alone or in combination with an inert water-
 miscible organic solvent such as methanol, ethanol or
 dioxane.
 . . .
 in the PCT
 application, TER 231 is especially susceptible to
 cleavage by GST M1a-1a; TER 303 is especially susceptible
 to cleavage by A1-1; TER 286 is particularly
 susceptible
 to cleavage by P1-1 and A1-1, while TER 296 is

selectively cleaved by P1 Thus, in treating a tumor having elevated levels of P1 use of a compound of formula (1) having the tripeptide contained in TER 296 or TER 286 would be preferred. The relevant isoenzyme, GST P1-1 is elevated in more than 75% of human tumor specimens from breast, lung, liver. . .

L18 ANSWER 3 OF 5 PCTFULL COPYRIGHT 2006 Univentio on STN

DETD . . . toxic effect of TER199 in contrast to its unesterified form on HT4-1 cells, Figure 2 is a graph showing the effect of various combinations of chlorambucil either alone or in combination with ethacrynic acid or TER199.

. . . in tumor cells. Third, the compounds of formula (1) directly potentiate the effect of chemotherapeutic agents in the destruction of tumor cells. This combination of qualities makes the compounds of the invention useful both as hematopoiesis potentiating agents directly and to ameliorate the negative effects of chemotherapeutic. . .

. . . CMB, reducing the concentration CMB needed for 50% cell killing by a DMF of 1,08, In contrast the diethyl ester of 7E-C(Bz)-qG (TER 199) at only 12.5 pM enhanced CMB cytotoxicity by a factor of 1
Preferential expression of GST isoenzyme P1-1 has been reported in a. . .

. . . 5 when TER199 was administered along with the melphalan, the tumor volume mean was approximately 55% of control. For group 4 administered a combination of melphalan and ethacrynic acid, the volumes were approximately 35% of control. Thus, both ethacrynic acid and TER199 potentiate the effects of. . .

. . . GM-CSFI G-CSFI M-CSFI Flt3/Flk-2 and Steel factor (stem cell factor/c-kit ligand). Of particular interest was the finding that TER199 enhances colony formation stimulated by combinations of cytokines. Additionally, the enhancing effect is more pronounced in human than in murine bone marrow, These results suggest that TER199 has. . .

. . . (60)* 65±4 (44)* 67±5 (49)*

50ng)

'Statistically significant

Table 5: Influence of TER199 on colony formation by normal human bone marrow GM-progenitor cells stimulated by combinations of cytokines.

L18 ANSWER 4 OF 5 PCTFULL COPYRIGHT 2006 Univentio on STN

DETD Properties and Distribution of GST Isoenzymes
The various GST isoenzymes are dimeric proteins formed by binary combinations of monomers encoded by at least fifteen known genes in four gene families, resulting in the theoretical possibility of several dozen different. . .

. . . availability of a substantial family of isoenzymes which is unevenly distributed as to its members with respect to normal and tumor tissue, combined with differences

between the family members in substrate specificity and inhibitor sensitivity, makes this family an important target for designing therapies for conditions. . . .

Figures 3a and 3b are graphs showing the decomposition of TER 286 and TER 322 by various GSTs.

Figure 5 shows the effect of TER 286 on growth of tumors in mice.

Figure 6 shows the effect of 100-200 mg/kg TER 286 on the GM-CFU in bone marrow of mice.

Figure 7 shows the dose-dependence of bone marrow GM-CFU for administration of TER 286.

Modes of Carrying Out the Invention

The compounds of Formula (1) are prodrugs which can be used selectively to target tissues having. . . specificity to the prodrug

provided. As shown below, the prodrugs prepared for illustration, TER 230, as a model compound, and TER 231, TER

286, TER 296 and TER 303 as effective prodrugs, are differentially activated by GST enzymes of the A, 7 and a classes. These. . . .

T-Glutamyl-a-Amino-o-((2-ethyl-N,N,N,N-tetra(2'-chloro)ethylphosphoramidate)sulfonyl)propionylglycine, (TER 231);

is

T-Glutamyl-a-Amino-o-((2-ethyl-N,N,N,N-tetra(21-chloro)ethylphosphoramidate)sulfonyl)propionyl-(R)-(-)-phenylglycine (TER 286);

T-Glutamyl-a-Amino-fl-((2-ethyl-N,N,N,N-tetra(21-chloro)ethylphosphoramidate)sulfonyl)propionyl-phenylalanine (TER 303);

7-Glutamyl-a-amino-O-(i-phenyl, 2-ethyl-N,N,N,N-tetra(21-chloroethyl)phosphoramidate)sulfonyl)propionyl glycine. (TER 296);

T-Glutamyl-a-amino-fl-(i-phenyl, 2-ethyl-N,N,N,N-tetra(21-chloroethyl)phosphoramidate)sulfonyl)propionyl (R)-(-)-phenylglycine (TER 297);

T-Glutamyl-u-amino-fl(2-ethyl, N,N-bis(2'-chloroethyl)carbamoyle)sulfonyl)propionyl glycine (TER 322) and its diethyl ester (TER 325); and

T-Glutamyl-u-amino-fl-((2-ethyl-(4-benzyloxy(N,.N,N',N' tetrakis(2-chloroethyl)phosphorodiamidate)) carbamido)sulfonyl)propionyl glycine.

base or

acid at a temperature of from about 00C to about 1000C, preferably at room temperature either in water alone or in combination with an inert water-miscible organic solvent such as methanol, ethanol or dioxane.

the

compounds exemplified below, TER 231 is especially susceptible to cleavage by GST M1a-1a; TER 303 is especially susceptible to cleavage by A1-1; TER 286 is particularly susceptible to

cleavage by P1-1 and A1-1, while TER 296 is selectively cleaved by P1. Thus, in treating a tumor. . . tumor, they appear to stimulate GM progenitors in bone marrow. There is relatively

little organ toxicity and no evidence of leukocytosis. For TER 286, the relevant isoenzyme, GST P1-1 is elevated in more than 75% of human tumor specimens from breast, lung, liver and colon.

synthesis of TER 296 or TER

297, α -amino- β -l-sulfhydryl phenylpropionic acid is substituted for the cysteine residue in the analog. For the synthesis of

TER 286, phenylglycine is substituted for glycine in the tripeptide as AAC. For synthesis of TER 303, phenyl alanine is substituted for glycine as. . .

a sep. funnel,

and separated. The lower organic layer was saved, and the aqueous layer was extracted with 100 ml of CH₂Cl₂. The combined organic phases were washed with 500 ml saturated brine and dried over Na₂SO₄. The solution was filtered and reduced to an oil under. . .

to separate. The lower organic layer was removed and saved, and the upper layer was extracted with 100 ml CH₂Cl₂. The combined CH₂Cl₂ layers were washed six times with 100 ml portions

- 25

of saturated NaCl and dried over Na₂SO₄- The solution was filtered and. . .

9:1. The reaction was

quenched with dropwise addition of 100 ml water, and extracted twice with 250 ml portions of EtOAc. The combined organic extracts were washed twice with 100 ml portions of brine and dried over Na₂SO₄. This was filtered and evaporated to 8.3. . .

stirred overnight. The mixture was poured into 35 ml of water and extracted with two 50 ml portions of toluene, and the combined organic phases were dried over Na₂SO₄ and concentrated to a viscous oil. TLC (9:1 EtOAc:MeOH) showed one spot, rf 0 UV active.. .

T-Glutamyl-u-Amino-o-((2-ethyl, -N,N,N,N-tetra(21-chloro). ethylphosphoramidate)sulfonyl)propionyl-(R)-(-)-phenylglycine (TER 286);

T-Glutamyl-u-Amino-o-((2-ethyl-N,N,N,N-tetra(2'-chloro)ethylphosphoramidate)sulfonyl)propionyl-phenylalanine (TER 303);

T-Glutamyl-u-Amino-O-(1-phenyl, (2-ethyl-N,N,N,N-tetra(2-chloro)ethylphosphoramidate)sulfonyl) propionyl glycine (TER 296);

T-Glutamyl-u-Amino (1-phenyl, (2-ethyl-N,N,N,N-tetra(21-chloro)ethylphosphoramidate)sulfonyl) propionyl (R)-(-)-phenylglycine (TER 297).

Further details with respect to TER 286 are as follows.

TER 286 was similarly tested with the results shown in

Figure 3a. Both P1-1 and A1-1 accelerate the cleavage of TER 286 roughly six times faster than background; there is negligible acceleration of cleavage with M1a-1a.

prodrug

selected, specificity can be obtained for any of the three human GSTs tested. Thus, TER 29G is selectively cleaved by P1-1; TER

286 is selectively cleaved by P1-1 and A1-1; TER 303 is

selectively cleaved by Al-1; and TER 231 by Mla-la.

when

MCF-7 tumor cells transfected by Pl-1 were compared to cells transfected only with the control vector. As shown in Figure 4a, when TER 286 is employed, cells containing high Pl-1 enzyme

levels are sensitized 4-fold to the prodrug compared to controls; Figure 4b shows a 2-fold.

were obtained for MCF-7 cells which are sensitive to CTX as compared to CTX-resistant forms. The CTX-resistant cells were more sensitive to TER 286 by a factor

of 1.8 as compared to cells sensitive to CTX in a standard clonogenic assay.

In Figure 5, the squares represent controls; circles represent 300 mg/kg of TER 286; triangles represent 400 mg/kg of the same drug. The points shown are the mean + SEM of 5-7 mice per group.

Example 6

Effect of Prodrug on Bone Marrow

In the assay, B6D2F1 mice were treated with various doses of TER 286 intraperitoneally either as a single injection or as five daily injections. Femoral bone marrows were harvested 24 hours later and assayed for. . . results are shown in Figure 6. Increases up to 1800i of controls for GM-CFU were obtained with administration of 100-200 mg/kg of TER 286; the values shown are the mean plus SD of 2-3 experiments.

Further, as shown in Figure 7, the optimum dosage range appears to be in this region of 100-200 mg/kg for TER 286.

L18 ANSWER 5 OF 5 PCTFULL COPYRIGHT 2006 Univentio on STN

DETD Properties and Distribution of GST Isoenzymes

The various GST isoenzymes are dimeric proteins formed by binary combinations of monomers encoded by at least fifteen known genes in four gene families, resulting in the theoretical possibility of several dozen different.

availability of a substantial family of isoenzymes which is unevenly distributed as to its members with respect to normal and tumor tissue, combined with differences between the family members in substrate specificity and inhibitor sensitivity, makes this family an important target for designing therapies for conditions.

2 is a graph showing the decomposition of TER 231 by various GSTs,

Figure 3 is a graph showing the decomposition of TER 286 by various GSTs.

for various chemotherapeutic agents with respect to cells having high or low levels of GST Pl

Figure 5 shows the effect of TER 286 on growth of tumors in mice.

Figure 6 shows the effect of 100-200 mg/kg TER 286 on the GM-CFU in bone marrow of mice.

Figure 7 shows the dose-dependence of bone marrow GM-CFU for administration of TER 286.

Modes of Carrying Out the Inventio

The compounds of Formula (1) are prodrugs which can be used selectively to target tissues having . . . specificity to the prodrug

provided. As shown below, the prodrugs prepared for illustration, TER 230, as a model compound, and TER 231, TER

286, TER 296 and TER 303 as effective prodrugs, are differentially activated by GST enzymes of the A, w and a classes. These. . .

T-Glutamyl-a-Amino-fl-((2-ethyl-N,N,N,N-tetra(21-chloro)ethylphosphoramidate)sulfonyl)propionylglycine, (TER 231)1
7-Glutamyl-a-Amino-O-((2-ethyl-N,N,N,N-tetra(21-chloro)ethylphosphoramidate)sulfonyl)propionyl-(R)-(-)-phenylglycine (TER 286);

- 13 -

oy-Glutamyl-oi-Amino-O-((2-ethyl-N,N,N,N-tetra(21-chloro)ethylphosphoramidate)sulfonyl)propionyl-phenylalanine (TER 303);

T-Glutamyl-a-Amino-fl-(I-phenyl, 2-ethyl-N,N,N,N-tetra(21-chloro)ethylphosphoramidate)sulfonyl)propionyl glycine (TER 296);

7-Glutamyl-u-Amino-fl-(1-phenyl, 2-ethyl-N,N,N,N-tetra(21-chloro)ethylphosphoramidate)sulfonyl)propionyl (R)-(-)-phenylglycine (TER 297).

base or

acid at a temperature of from about 00C to about 1000C, preferably at room temperature either in water alone or in combination with an inert water-miscible organic solvent such as methanol, ethanol or dioxane.

exemplified below, TER 231 is especially susceptible 5 to cleavage by GST Mla-la; TER 303 is especially susceptible to cleavage by Al-1; TER 286 is particularly susceptible to

cleavage by Pl-1 and Al-1, while TER 296 is selectively cleaved by PI Thus, in treating a tumor. . . tumor, they appear to stimulate GM progenitors in bone marrow, There is relatively little organ toxicity and no evidence of leukocytosis, For TER

286, the relevant isoenzyme, GST PI-1 is elevated in more than 75% of human tumor specimens from breast, lung, liver and colon.

for synthesis of TER 296 or TER

297, a-amino-o-sulphydryl-o-phenylpropionic acid is substituted for the cysteine residue in the analog. For the synthesis of

TER 286, phenylglycine is substituted for glycine in the

tripeptide as AAC. For synthesis of TER 303, phenyl alanine is substituted for glycine as. . .

sep. funnel,

and separated. The lower organic layer was saved, and the aqueous layer was extracted with 100 ml of CH₂CL₂. The combined organic phases were washed with 500 ml saturated brine and dried over Na₂SO₄. The solution was filtered and reduced to an oil

under. . .

to separate. The lower organic layer was removed and 35 saved, and the upper layer was extracted with 100 ml CH₂Cl₂. The combined CH₂Cl₂ layers were washed six times with 100 ml portions

- 23

of saturated NaCl, and dried over Na₂SO₄- The solution was filtered. . .

9:1. The reaction was quenched with dropwise addition of 100 ml water, and extracted twice with 250 ml portions of EtOAc. The combined organic extracts were washed twice with 100 ml portions of brine and dried over Na₂SO₄. This was filtered and evaporated to 8.3. . .

stirred overnight. The mixture was poured into 35 ml of water and extracted with two 50 ml portions of toluene, and the combined organic phases were dried over Na₂SO₄ and concentrated to a viscous oil. TLC (9:1 EtOAc:MeOH) showed one spot, *rf* 0,7, UV active.. . .

7-Glutamyl-u-Amino-g-((2-ethyl-N,N,N,N-tetra(21-chloro) ethylphosphoramidate)sulfonyl)propionyl-(R)-(-)-phenylglycine (TER 286);

7-Glutamyl-a-Amino-fl-((2-ethyl-N,N,N,N-tetra(21-chloro)ethylphosphoramidate)sulfonyl)propionyl-phenylalanine (TER 303);

7-Glutamyl-a-Amino (1-phenyl, (2-ethyl-N,N,N,N-tetra(21-chloro)ethylphosphoramidate)sulfonyl) propionyl glycine (TER 296);

7-Glutamyl-a-Amino-fl-(1-phenyl, (2-ethyl-N,N,N,N-tetra(21-chloro)ethylphosphoramidate)sulfonyl) propionyl (R)-(-)-phenylglycine (TER 297).

Further details with respect to TER 286 may be found in Lyttle, M.H. et al. J Med Chem (1994) 37:1501-1507; Lyttle, M. et al, J Med Chem (1994) 34:189. . .

TER 286 was similarly tested with the results shown in

Figure 3. Both PI-1 and Al-1 accelerate the cleavage of TER 286

roughly six times faster than background; there is negligible acceleration of cleavage with Mla-la.

when

MCF-7 tumor cells transfected by PI-1 were compared to cells transfected only with the control vector. As shown in Figure 4a, when TER 286 is employed, cells containing high PI-1 enzyme

levels are sensitized 4-fold to the prodrug compared to controls; Figure 4b shows a 2-fold. . .

obtained for MCF-7 cells which are sensitive to CTX as compared to CTX-resistant forms. The 25 CTX-resistant cells were more sensitive to TER 286 by a factor of 1,8 as compared to cells sensitive to CTX in a standard clonogenic assay.

- 33 -

In Figure 5, the squares represent controls; circles represent 300 mg/kg of-TER 286; triangles represent 400 mg/kg of the same

drug. The points shown are the mean \pm SEM of 5-7 mice per group.

Example 6

Effect of Prodrug on Bone Marrow

In the assay, B6D2F. mice were treated with various doses of TER 286 intraperitoneally either as a single injection or as five daily injections. Femoral bone marrows were harvested 24 hours later and assayed for. . . results are shown in Figure 6, Increases up to 18016 of controls for GM-CPU were obtained with administration of 100-200 mg/kg of TER 286; the values shown are the mean plus SD of 2-3 experiments.

Further, as shown in Figure 7, the optimum dosage range appears to be in this region of 100-200 mg/kg for TER 286.

=> s cancer? or tumor? or neoplas?

80405 CANCER?

67062 TUMOR?

23301 NEOPLAS?

L19 100034 CANCER? OR TUMOR? OR NEOPLAS?

=> s l19/clm

23115 CANCER?/CLM

15601 TUMOR?/CLM

3791 NEOPLAS?/CLM

L20 32848 (CANCER?/CLM OR TUMOR?/CLM OR NEOPLAS?/CLM)

=> s l20 and l18

L21 2 L20 AND L18

=> d ibib 1-2

L21 ANSWER 1 OF 2 PCTFULL COPYRIGHT 2006 Univentio on STN
ACCESSION NUMBER: 1999037802 PCTFULL ED 20020515
TITLE (ENGLISH): METHODS TO IDENTIFY MYEOSTIMULANTS
TITLE (FRENCH): METHODES D'IDENTIFICATION DE MYEOSTIMULANTS
INVENTOR(S): KAUVAR, Lawrence, M.
PATENT ASSIGNEE(S): TELIK, INC.
LANGUAGE OF PUBL.: English
DOCUMENT TYPE: Patent
PATENT INFORMATION:

NUMBER	KIND	DATE
WO 9937802	A1	19990729

DESIGNATED STATES

W:

AU CA GD IN JP AT BE CH CY DE DK ES FI FR GB GR IE IT
LU MC NL PT SE

APPLICATION INFO.:

WO 1999-US765 A 19990114

PRIORITY INFO.:

US 1998-09/010,390 19980121

L21 ANSWER 2 OF 2

PCTFULL COPYRIGHT 2006 Univentio on STN

ACCESSION NUMBER:

1995009865 PCTFULL ED 20020514

TITLE (ENGLISH):

GLUTATHIONE S-TRANSFERASE-ACTIVATED COMPOUNDS

TITLE (FRENCH):

COMPOSES ACTIVES PAR LA GLUTATHIONE S-TRANSFERASE

INVENTOR(S):

KAUVAR, Lawrence, M.;

LYTTLE, Matthew, H.;

SATYAM, Apparao

PATENT ASSIGNEE(S):

TERRAPIN TECHNOLOGIES, INC.

LANGUAGE OF PUBL.:

English

DOCUMENT TYPE: Patent
PATENT INFORMATION:

	NUMBER	KIND	DATE
DESIGNATED STATES	WO 9509865	A1	19950413
W:	AU CA JP AT BE CH DE DK ES FR GB GR IE IT LU MC NL PT		
SE			
APPLICATION INFO.:	WO 1994-US10796	A	19940923
PRIORITY INFO.:	US 1993-8/130,736		19931001
	US 1994-8/130,736		19940919

=> s 119 and 18

'RN' IS NOT A VALID FIELD CODE

452833 COMBINATION

199923 COMBINATIONS

492208 COMBINATION

(COMBINATION OR COMBINATIONS)

0 439943-59-6/RN

429338 PY>2002

L22 0 L19 AND L8

=> s 119 and 118

L23 5 L19 AND L18

=> d kwic 3

L23 ANSWER 3 OF 5 PCTFULL COPYRIGHT 2006 Univentio on STN

DETD . . . effects

can be neutropenia, thrombocytopenia and immune suppression generally. These side effects are not only unpleasant, but they also restrict the efficacy of cancer therapy and place the subject at serious risk of infection and uncontrolled bleeding.

Disclosure of the Invention

The invention provides compounds which are useful in modulating hematopoiesis generally and as aids to chemotherapeutic treatment of tumors by virtue of their ability to exert a protective effect on the hematopoietic system with respect to toxic agents which are otherwise useful. . .

cell populations in the course of bone marrow transplantation. The invention is further directed to the use of compounds of the invention as tumor-specific chemo- or radiosensitizers, thus potentiating the effect of treatment, and as generalized chemoprotectants,

The invention also includes pharmaceutical compositions containing the compounds of the. . .

Brief Description of the Drawings

Figure 1a shows the effect of TER199 on the survival of tumor cells treated with various concentrations of chlorambucil.

toxic effect of TER199 in contrast to its unesterified form on HT4-1 cells, Figure 2 is a graph showing the effect of various combinations of chlorambucil either alone or in combination with ethacrynic acid or TER199.

chemotherapeutic agents, Second, they usually inhibit at least one class of the GST isoenzymes, including the n subclass, which is particularly prevalent in tumor cells. Third, the compounds of formula (1) directly potentiate the effect of chemotherapeutic agents in the destruction of tumor cells. This combination of qualities makes the compounds of the invention useful both as hematopoiesis potentiating agents directly and to ameliorate the negative effects of chemotherapeutic. . . .

Example 1

Use of the Compounds of the Invention in Potentiation of Cytotoxic Agents in Human Cells

This example describes: 1) potentiation in human tumor cells of a cytotoxic agent currently used in cancer

chemotherapy by GST inhibitors, including compounds of the present invention, as well as 2) enhanced intracellular efficacy of esterified forms of these compounds,

HT-29 (human colon adenocarcinoma) cells were obtained from Dr, Roberto Ceriani (Cancer Research Fund of Contra Costa County, Walnut Creek, CA) and were used in log phase of growth unless otherwise specified.

The results in Tables 1-3 show that several GSH analogs found to be inhibitors of GSH also potentiate killing of human tumor cells in culture by CMB which is a substrate for various GSTs. Results of potentiation tests with several GST inhibitors in HT29. . . .

CMB, reducing the concentration CMB needed for 50% cell killing by a DMF of 1,08, In contrast the diethyl ester of 7E-C(Bz)-qG (TER 199) at only 12.5 pM enhanced CMB cytotoxicity by a factor of 1

Preferential expression of GST isoenzyme P1-1 has been reported in a range of human tumors. In the present study the efficacy of CMB potentiation of the several GST inhibitors tested correlated directly with their

- 18 -

potencies as. . . .

Example 2

Potentiation of Melphalan Toxicity in vivo

Male scid mice were subcutaneously implanted with HT4-1 tumors from donor mice. HT4-1 is a subclone of HT-29, a human colon cancer. When tumors reached approximately 100 MM3, the mice were randomized into six treatment groups and treated for seven days as follows.

The mice were monitored for weight changes and tumor volumes were determined by measurement with calipers.

The tumor growth was monitored until the average tumor size reached 1500 MM3 for all groups except melphalan with ethacrynic acid. This group failed to reach this volume even after 72 days.

The results were computed in terms of the tumor volume in the drug treated mice as a percentage of control tumor volume (i.e., in the group administered vehicle alone). In group 11 administered melphalan alone, the tumors were approximately 75% of the volume of

controls. In group 5 when TER199 was administered along with the melphalan, the tumor volume mean was approximately 55% of control. For group 4 administered a combination of melphalan and ethacrynic acid, the volumes were approximately 35% of control. Thus, both ethacrynic acid and TER199 potentiate the effects of melphalan, (The volume measurements were taken at the time control tumors reached 1500 nun3

Example 3

Metabolic Effects of the Invention Compounds

The metabolic effects related to toxicity of the compounds of the invention on. . .

PG intraperitoneally. Femoral bone marrows were harvested 24 hours later and assayed for GM-CFU by the method of East, C.J. et. al. Cancer Chemother Pharmacol (1992) 31:123 An increase in the number of colonies in a dose-dependent manner up to a dosage of 90 mg/kg. . .

GM-CSFI G-CSFI M-CSFI

Flt3/Flk-2 and Steel factor (stem cell factor/c-kit ligand). Of particular interest was the finding that TER199 enhances colony formation stimulated by combinations of cytokines. Additionally, the enhancing effect is more pronounced in human than in murine bone marrow, These results suggest that TER199 has. . .

(60)* 65±4 (44)* 67±5 (49)* 50ng)

'Statistically significant

Table 5: Influence of TER199 on colony formation by normal human bone marrow GM-progenitor cells stimulated by combinations of cytokines.

=>

---Logging off of STN---

=>

Executing the logoff script...

=> LOG Y

COST IN U.S. DOLLARS	SINCE FILE	TOTAL
	ENTRY	SESSION
FULL ESTIMATED COST	20.52	82.49
DISCOUNT AMOUNTS (FOR QUALIFYING ACCOUNTS)	SINCE FILE	TOTAL
	ENTRY	SESSION
CA SUBSCRIBER PRICE	0.00	-2.25

STN INTERNATIONAL LOGOFF AT 09:45:04 ON 14 AUG 2006

Connecting via Winsock to STN

Welcome to STN International! Enter x:x

LOGINID:SSSPTA1642BJF

PASSWORD:

TERMINAL (ENTER 1, 2, 3, OR ?):2

* * * * * Welcome to STN International * * * * *

NEWS 1 Web Page URLs for STN Seminar Schedule - N. America
NEWS 2 "Ask CAS" for self-help around the clock
NEWS 3 FEB 27 New STN AnaVist pricing effective March 1, 2006
NEWS 4 APR 04 STN AnaVist \$500 visualization usage credit offered
NEWS 5 MAY 10 CA/CAPLUS enhanced with 1900-1906 U.S. patent records
NEWS 6 MAY 11 KOREAPAT updates resume
NEWS 7 MAY 19 Derwent World Patents Index to be reloaded and enhanced
NEWS 8 MAY 30 IPC 8 Rolled-up Core codes added to CA/CAPLUS and
USPATFULL/USPAT2
NEWS 9 MAY 30 The F-Term thesaurus is now available in CA/CAPLUS
NEWS 10 JUN 02 The first reclassification of IPC codes now complete in
INPADOC
NEWS 11 JUN 26 TULSA/TULSA2 reloaded and enhanced with new search and
and display fields
NEWS 12 JUN 28 Price changes in full-text patent databases EPFULL and PCTFULL
NEWS 13 JUL 11 CHEMSAFE reloaded and enhanced
NEWS 14 JUL 14 FSTA enhanced with Japanese patents
NEWS 15 JUL 19 Coverage of Research Disclosure reinstated in DWPI
NEWS 16 AUG 09 INSPEC enhanced with 1898-1968 archive

NEWS EXPRESS JUNE 30 CURRENT WINDOWS VERSION IS V8.01b, CURRENT
MACINTOSH VERSION IS V6.0c(ENG) AND V6.0Jc(JP),
AND CURRENT DISCOVER FILE IS DATED 26 JUNE 2006.

NEWS HOURS STN Operating Hours Plus Help Desk Availability
NEWS LOGIN Welcome Banner and News Items
NEWS IPC8 For general information regarding STN implementation of IPC 8
NEWS X25 X.25 communication option no longer available

Enter NEWS followed by the item number or name to see news on that
specific topic.

All use of STN is subject to the provisions of the STN Customer
agreement. Please note that this agreement limits use to scientific
research. Use for software development or design or implementation
of commercial gateways or other similar uses is prohibited and may
result in loss of user privileges and other penalties.

* * * * * STN Columbus * * * * *

FILE 'HOME' ENTERED AT 09:55:27 ON 14 AUG 2006

=> file reg

COST IN U.S. DOLLARS

SINCE FILE	TOTAL
ENTRY	SESSION
0.21	0.21

FULL ESTIMATED COST

FILE 'REGISTRY' ENTERED AT 09:55:37 ON 14 AUG 2006

USE IS SUBJECT TO THE TERMS OF YOUR STN CUSTOMER AGREEMENT.

PLEASE SEE "HELP USAGETERMS" FOR DETAILS.

COPYRIGHT (C) 2006 American Chemical Society (ACS)

Property values tagged with IC are from the ZIC/VINITI data file
provided by InfoChem.

STRUCTURE FILE UPDATES: 11 AUG 2006 HIGHEST RN 900864-99-5

DICTIONARY FILE UPDATES: 11 AUG 2006 HIGHEST RN 900864-99-5

New CAS Information Use Policies, enter HELP USAGETERMS for details.

TSCA INFORMATION NOW CURRENT THROUGH January 6, 2006

Please note that search-term pricing does apply when
conducting SmartSELECT searches.

REGISTRY includes numerically searchable data for experimental and
predicted properties as well as tags indicating availability of
experimental property data in the original document. For information
on property searching in REGISTRY, refer to:

<http://www.cas.org/ONLINE/UG/regprops.html>

=> E "TER 199"/CN 25

E1	1	TER 17210/CN
E2	1	TER 183/CN
E3	1 -->	TER 199/CN
E4	1	TER 200/CN
E5	1	TER 206/CN
E6	1	TER 211/CN
E7	1	TER 230/CN
E8	1	TER 231/CN
E9	1	TER 286/CN
E10	1	TER 317/CN
E11	1	TER 322/CN
E12	1	TER 324/CN
E13	1	TER 338/CN
E14	1	TER 3938/CN
E15	1	TER 838/CN
E16	1	TER 838, POLYMER WITH TEDIMON 316/CN
E17	1	TER 930180/CN
E18	1	TER BINDING PROTEIN (PLASMID RTS1 GENE ORF91)/CN
E19	1	TER HELL 5603/CN
E20	1	TER HELL 6805/CN
E21	5	TER(5,6)FULLERENE-C50-D5H(6)/CN
E22	3	TER(5,6)FULLERENE-C50-D5H(6), DOCOSAHYDRO-/CN
E23	2	TER(5,6)FULLERENE-C50-D5H(6), OCTADECALHYDRO-/CN
E24	1	TER-1H-INDOLE, 2,2',2'',3,3',3'''-HEXAPHENYL-/CN
E25	1	TER-9H-CARBAZOLE/CN

=> S E3

L1 1 "TER 199"/CN

=> DIS L1 1 SQIDE

THE ESTIMATED COST FOR THIS REQUEST IS 6.36 U.S. DOLLARS
DO YOU WANT TO CONTINUE WITH THIS REQUEST? (Y)/N:Y

L1 ANSWER 1 OF 1 REGISTRY COPYRIGHT 2006 ACS on STN

RN 168682-53-9 REGISTRY

CN Glycine, L- γ -glutamyl-S-(phenylmethyl)-L-cysteinyl-2-phenyl-,
diethyl ester, (2R)- (9CI) (CA INDEX NAME)

OTHER CA INDEX NAMES:

CN Glycine, N-[N-L- γ -glutamyl-S-(phenylmethyl)-L-cysteinyl]-D-2-phenyl-,
diethyl ester

OTHER NAMES:

CN Ter 199

CN Terrapin 199

CN TLK 199

FS STEREOSEARCH

MF C27 H35 N3 O6 S

CI COM

SR CA

LC STN Files: ADISINSIGHT, BIOSIS, CA, CAPLUS, DDFU, DRUGU, IMSDRUGNEWS,
IMSPATENTS, IMSRESEARCH, PHAR, PROUSDDR, TOXCENTER, USPAT2, USPATFULL
DT.CA Caplus document type: Journal; Patent
RL.P Roles from patents: BIOL (Biological study); PREP (Preparation); USES
(Uses)
RL.NP Roles from non-patents: BIOL (Biological study); USES (Uses)

Absolute stereochemistry.

/ Structure 2 in file .gra /

PROPERTY DATA AVAILABLE IN THE 'PROP' FORMAT

17 REFERENCES IN FILE CA (1907 TO DATE)
17 REFERENCES IN FILE CAPLUS (1907 TO DATE)

=>

---Logging off of STN---

=>

Executing the logoff script...

=> LOG Y

COST IN U.S. DOLLARS	SINCE FILE	TOTAL
FULL ESTIMATED COST	ENTRY	SESSION
	7.10	7.31

STN INTERNATIONAL LOGOFF AT 09:56:27 ON 14 AUG 2006